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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
10/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/729,056	GRAINGER ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *153,154,157-165,174-176 and 181-184* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *153,154,157-165,174-176 and 181-184* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/12/2009 has been entered. The examiner notes the receipt of the amendments and remarks received in the office on 8/12/2009 amending claims 153, 154, 174, 175 and adding new claims 183, 184. Claims 1-152, 155-156, 166-173, 177-180 have been canceled. Claims 153, 154, 157-165, 174-176, 181-184 are pending and are being examined on the merits herein.

Response to Remarks/Arguments

Applicants' arguments and the declaration by Dr. Grainger with respect to the filing date and the subject matter of the instant application has been fully considered and found to be persuasive with respect to 102 and 103 rejections. Accordingly those rejections have been withdrawn. Applicants' claim (claims 181-184) regarding a stilbene antisteroid, a 1, 2 diphenylethane antisteroid, or a naphthalene antisteroid in treating a cardiovascular indication has a priority date of 6/7/1995. Applicants' state that as neither the present application nor the '775 application has been allowed, no terminal disclaimer is required at this time. Should a terminal disclaimer be required, the Office may request it upon a notice of allowable subject matter in either the present application or the '775 application. Accordingly, the ODP rejection is maintained and is given below for

Applicants' convenience. Applicants' argue (regarding the 112(1) enablement rejection) that the Applicant has enabled the claimed methods and it is within the skill of the art worker in the relevant art to determine the amount of agent and route of administration, as well as an appropriate mode to test agents. This is not found to be persuasive because the claims for treating a cardiovascular indication such as stroke, thrombosis are not enabled because of the reasons given below in the enablement rejection and also the specification does not teach administration of any of the claimed compounds (including stilbene antisteroid, 1, 2 diphenyl ethane antisteroid etc as claimed in claims 181-184) in treating cardiovascular indication in mammals. Applicants' amendments, further search and consideration necessitated the following rejections in this office action. Accordingly, the action is made non-Final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 153, 154, 157-165, 169-175, 181, 182 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 173-194,196-203, 205-211 and 231 of copending Application No.

09/754,775. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the method claimed in claims 153, 154, 157-165, 169-175 of the instant application utilizes the same biological pathway comprising increasing the level of TGF-beta encompassing utilizes the same active agents in the method of claim 173 of the co-pending application. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the diseases and the agents claimed in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 153, 154, 159, 160, 165, 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,472,985. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teaches a method of inhibiting proliferation of smooth muscle cells in conditions selected from atherosclerosis, thrombosis, stroke, myocardial infarction in a mammal comprising administering structural analogs of tamoxifen effective to activate or stimulate production of TGF-beta. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents

claimed by Applicants in the co-pending application and hence renders obvious over the diseases and the agents claimed in the co-pending application.

Claims 174, 175, 183, 184 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9, 11, 13 and 15 of U.S. Patent No. 5,599, 844. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teaches a method of treating vascular trauma by inhibiting proliferation of vascular smooth muscle cells in a mammal comprising administering structural analogs of tamoxifen effective to elevate TGF-beta. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the diseases and the agents claimed in the co-pending application.

Claims 153, 154, 159, 160, 165, 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4 of U.S. Patent No. 5,773,479. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating atherosclerosis condition in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the

therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the disease and the agents claimed in the co-pending application.

Claims 153, 154, 159, 160, 165, 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 9, 10, 11 of U.S. Patent No. 5,847,007. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating atherosclerosis condition in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the disease and the agents claimed in the co-pending application.

Claims 153, 154, 159, 160, 165, 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10 of U.S. Patent No. 6,166,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating atherosclerosis in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic

agents claimed by Applicants in the co-pending application and hence renders obvious over the disease and the agents claimed in the co-pending application.

Claims 153, 154, 159, 160, 165, 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 19, 27, 30-37, 38, 39, 41, 42 of U.S. Patent No. 6,251,920. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating a condition selected from atherosclerosis, stroke, thrombosis, myocardial infarction condition in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the disease and the agents claimed in the co-pending application.

Claims 153, 154, 159, 160, 165, 181-182 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 17 of U.S. Patent No. 6,262,079 Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of inhibiting vascular smooth muscle cell proliferation in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of inhibiting smooth muscle cells administering

the therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the disease and the agents claimed in the co-pending application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 153-154, 157-165, 169-184 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not teach administration of any of the claimed compounds in treating any of the cardiovascular indication in mammals as listed in the claims. The compounds claimed in treating cardiovascular indication have different biological activities, bioavailabilities, pharmacokinetic profiles, and pharmacological efficacy and does not reasonably provide enablement for a therapeutic method of treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter. The prior art as shown below in 'state of the art' section teaches the adverse role of tamoxifen in conditions like thrombosis, and stroke. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required

undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a therapeutic method of treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that is a structural analog of tamoxifen (claims 153, 154, 157-165, 174-176, 181-184), a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene antisteroid (181-184) b) administering a cytostatic dose of the agent to the mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis so as to inhibit smooth muscle cell proliferation, inhibit plaque (claims 153, 154, 157-165), inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof (claims 181-184).

(5) Breadth of the Claims:

The claims (181-84) are broad and embrace treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation that is a structural analog of tamoxifen, a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene

antisteroid b) administering a cytostatic dose of the agent to the mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof. The claims are broad with respect to the different agents claimed because there are a number of structural analogs of tamoxifen, stilbene antisteroids, 1, 2 diphenylethane antisteroids and naphthalene antisteroids known and yet to be discovered.

(6)/(7) Guidance of the Specification and Working Examples

The specification provides guidance and working examples related to: 1) impact of Tamoxifen on Vascular Smooth Muscle Cells and the Relationship thereof to TGF-Beta Production and Activation Cell culture, DNA synthesis assay and cell counting (2) heparin Effect on VSMC Proliferation and Differentiation (3) comparison of Enzyme-Dispersed and Explant-Derived Human VSMC (4) TGF-beta and Transgenic apo(a) Mice - used to study whether inhibition of TGF-beta activation, resulting in enhanced VSMC proliferation, represents a key step in atherogenesis (5) Tamoxifen Inhibits Migration and Lipid Uptake in VSMC in vitro and in Transgenic Mice (6) Effect of Idoxifene on Cultured Human VSMCs (7) Tamoxifen elevates TGF-.beta. and suppresses diet-induced formation of lipid lesions in mouse aortae (8) Determination of Active and Acid Activatable TGF-.beta. in Human Sera, Platelets and Plasma by Enzyme-Linked Immunosorbent Assays (9) Association of TGF-beta with Lipoprotein Particles. However, there are no working examples and the specification does not teach administration of claimed agent(s) to a mammal in general or to a mammal with

decreased lumen diameter as a result of atherosclerosis, myocardial infarction or thrombosis.

(2/4) State/Predictability of the Art:

There is prior art teachings regarding lowering serum level cholesterol levels thereby treating or improving atherosclerotic conditions comprising administering to patients raloxifene (Black et al. U.S. 5,464,845), droloxifene (Fontana U.S. 5,426,123). The method of treating lipid accumulation, increase plaque stability comprising administering agents that include tamoxifen, tamoxifen analogs is predictable from the prior art. However, it is not predictable from the prior art that all known and yet to discover compounds of class, stibene antisteroids, naphthalene antisteroids etc will be useful in a method of treating a cardiovascular indication characterized by a decreased lumen diameter as there are teachings that relate to the side effects or toxic effects of drugs like hexesterol, clomiphene. Biofarma document (www.biofarma.kiev.ua\) teaches hexesterol's side effects include nausea, vomiting, vertigo and an administration of large/high doses cause toxic liver injury, excessive endometrium proliferation etc and the contraindications include diseases of the liver and kidney, malignant and benignant neoplasms in women under to , diseases connected with heightened level of blood coagulation etc and there are drug interactions involved with other medicinal products such as progesterone, pregnin etc. The document regarding clomiphene (drugs.com, clomiphene citrate) teaches that patients with liver disease, have undiagnosed vaginal bleeding, endometriosis, ovarian cysts etc should not take clomiphene and further teach that the side effects include allergy reactions, ovarian hyperstimulation syndrome etc.

Also, the prior art by Barath et al. (U.S. 5,242,397, filing date Jun 2 1992) teaches a method of treating a blood vessel that contains an atherosclerotic lesion by administration of an agent such as tamoxifen (col. 6, claims 1, 2). The prior art by Nakagawa et al. (Angiology, 1994, May 45, 5, 333-8) teaches a case of myocardial infarction, intracoronary thrombosis in two major arteries due to hormone therapy that included administration of 30 mg of tamoxifen. Dahan et al. in The Lancet, Mar 16 1985 teaches venous and arterial thrombosis in patients on tamoxifen therapy. Nevasaari in The Lancet, Oct 28, 1978 teaches that contraindications to the use of oestrogens included thromboembolic disorders and further states that four patients with metastatic breast cancer have had deepvein thromophelebilits while taking drug tamoxifen. Levine in P 406 (The NEJM, 1988, 404-407) states that Tamoxifen, an antiestrogenic agent has been reported to be associated with thromboembolism in patients with metastatic breast cancer. Also, the reference in the abstract teaches that chemotherapy contributes to thrombosis in patients with breast cancer. Also, Chlebowoski's teachings in Clin Breast Cancer, 2006, Feb 6, Suppl 2, S58-64 indicate that the clinical evidence suggests that tamoxifen increases stroke risk (see abstract). The reference teaches that women with breast cancer who were treated with tamoxifen had an 82% increased risk of ischemic stroke and a 29% increased risk of any stroke and tamoxifen has been shown to consistently increase the risk of stroke in randomized clinical trials (p S 60, col. 2, lines 2-6). McDonald et al. (BMJ, 303, 24 Aug 1991) teaches that women receiving adjuvant tamoxifen found a significant reduction in the incidence of myocardial infarction (p 436, discussion, col.2, para 2). However Rutqvist in p 258 (Recent Results

Cancer Res. , 1993, 257-66) (Other cardiovascular Effects, para 2) teaches that "In the Scottish Adjuvant Tamoxifen trial there was significant decreased incidence of myocardial infarction in patients in the tamoxifen group. However, other trials of similar size have not demonstrated such a benefit". It is not predictable from such prior art studies whether tamoxifen is useful in treating a cardiovascular indication such as stroke or thrombosis or myocardial infarction. Hence it is highly unpredictable to determine whether tamoxifen analogs would be useful in such diseases when tamoxifen a structurally agent has had either adverse effects (stroke, thrombosis) and mixed results (myocardial infarction) from the prior art and there is no data or studies provided in the specification to show that tamoxifen analogs would be useful in cardiovascular indications such as stroke or thrombosis or myocardial infarction.

(8) The Quantity of Experimentation Necessary:

In order to enable the instantly claimed methods that commensurate with the entire scope, a large quantity of experimentation would be necessary. With Applicants' guidance provided in the specification and what is known in the prior art the person of ordinary skill in the art would have to conduct experiments testing the compounds claimed for treating a cardiovascular indication. In order to practice the above claimed invention, one of ordinary skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human treatment, an appropriate animal model system to test the composition in a method of treatment of cardiovascular indication. If unsuccessful, one of ordinary skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model

system, or envision an entirely new combination of the above and test the system again. Considering the side effects, drug interactions and contraindications of compounds like clomiphene, hexesterol in the prior art this would be an arduous and daunting task. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a cardiovascular indication administering structural analog of tamoxifen, a stibene antisteroid, a 1, 3 diphenylethane antisterioid, or a napthalene antisteroid in a mammal. Also, the prior art and recent studies (see section state of the art) indicate that administration of tamoxifen has increased the risk of stroke and is associated with thrombosis. Accordingly, the subset of patient population who has breast cancer and a cardiovascular indication such as stroke or thrombosis upon administration will have a risk of having stroke or having thrombosis condition. It is known in the art that tamoxifen analogues such as iodotamoxifen or toremifene exhibit similar functional properties like tamoxifen as they are structurally similar. Hence it will be an undue experimentation to one having ordinary skill in the art to find which conditions and which subset of population are suitable for treating with tamoxifen analogues in a method of treating a cardiovascular indication such as stroke, thrombosis and myocardial infarction as claimed. Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 153, 154, 157-165, 174-176 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 153, 154, 174-175 has a limitation "inhibit plaque" is new matter and does not have support in the specification. The specification has support for "increasing plaque stability" but does not teach anywhere in description or data in examples inhibiting plaque.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 153, 154, 158, 160-163, 174-176, 181-184 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barath et al. (U.S. 5,242,397, filing date Jan 2 1992) and Thompson et al. (Br J Cancer, 1991, 63, 609-614) in view of Yang et al. (U.S. 5,219,548, filing date Oct 1 1990).

Barath et al. teaches a method of treating an atherosclerotic blood vessel comprising administering protein kinase c (PKC) inhibitors including tamoxifen (see abstract, col. 6, claims 1, 2). The reference teaches that inhibition of PKC by local delivery into the vessel wall of specific inhibitors prevents smooth muscle cell proliferation (col. 3, lines 18-20). The reference teaches that the protein kinase C inhibitor agents are useful in reducing the incidence of late restenosis attributed to cellular hyperplasia (abstract).

Thompson et al. teaches that treatment of breast cancer cell lines with tamoxifen results in the rise in TGF-beta1 mRNA expression. The reference in the Materials and Methods section teaches how to measure the level of TGF beta in tamoxifen treated tumors.

The references do not teach administration of tamoxifen analogs in treating a cardiovascular indication like atherosclerosis and does not teach selecting an agent for TGF-beta elevation

Yang et al. teaches synthesis of iodotamoxifen analogs of tamoxifen and state that the halogenated tamoxifen derivatives possess superior affinities to estrogen receptors (See abstract).

It would have been obvious to one having ordinary skill in the art at the time of the invention to have utilized the methods and materials from Thompson studies to measure the TGF beta level and select agents that elevate the TGF beta level. It would have been obvious to one having ordinary skill in the art from the studies of Thompson that tamoxifen elevated the levels of TGF-beta. Also, it would have been obvious from the studies of Barath et al. that the compound such as Tamoxifen is useful in treating an atherosclerotic condition. It would have been obvious to one having ordinary skill in the art at the time of the invention to have administered a structural analog of tamoxifen in a method of treating a cardiovascular indication such as atherosclerosis because of the prior art teachings of Barath et al. The reference teaches that atherosclerotic blood vessel can be treated by administration of PKC inhibitors including tamoxifen. One having ordinary skill in the art would have been motivated to administer a structural analog of tamoxifen such as 3 or 4-iodotamoxifen taught by Yang et al. because Yang teaches halogenated tamoxifen derivatives possess superior affinities to estrogen receptors. Also, one having ordinary skill in the art would have been motivated to administer a structural analog of tamoxifen such as 3 or 4-iodotamoxifen in expectation of success and in expectation of similar therapeutic benefits. Also, a *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical

structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). The references do not explicitly teach selecting a cytostatic dose of the agent as claimed by applicant. The dosage or selection of an agent or mode of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results.

Claims 153, 154, 158-163, 174-176, 181-184 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barath et al. (U.S. 5,242,397, filing date Jan 2 1992) and Thompson et al. (Br J Cancer, 1991, 63, 609-614).in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and Warri et al. (J Natl Cancer Inst. 1993, 85, 17, 1412)

Barath et al. and Thompson's teachings discussed as above.

The references do not teach administration of tamoxifen analogs in treating a cardiovascular indication like atherosclerosis and does not teach selecting an agent for TGF-beta elevation

Knabbe et al. teach the induction of transforming growth factor beta by the antiestrogen tamoxifen and analogs of tamoxifen, toremifene, droloxifene in vitro (See Abstract).

Warri et al. teach that elevated TGF beta 1 mRNA was observed in vitro and in vivo grown tumor cells treated with toremifene (see Abstract).

One having ordinary skill in the art at the time of the invention would have been motivated to select an analog of tamoxifen agent such as toremifene and administer to inhibit smooth muscle cell proliferation in expectation of success as well in effectively treating atherosclerosis. It would have been obvious to one having ordinary skill in the art at the time of the invention to have administered a structural analog of tamoxifen in a method of treating a cardiovascular indication such as atherosclerosis because of the prior art teachings of Barath et al. The reference teaches that atherosclerotic blood vessel can be treated by administration of PKC inhibitors including tamoxifen. Also, a *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). The references do not explicitly teach selecting a cytostatic dose of the agent as claimed by applicant. The dosage or selection of an agent or mode of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to

determine the optimal amount of ingredient to add in order to best achieve the desired results. The references do not teach oral or systemic administrations and the agent is administered in a sustained release form. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration (e.g oral, systemic) are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barath et al. (U.S. 5,242,397, filing date Jan 2 1992) and Thompson et al. (Br J Cancer, 1991, 63, 609-614) in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and Warri et al. (J Natl Cancer Inst. 1993, 85, 17, 1412) as applied to claims 153, 154, 158-163, 174-176, 181-184 above and further in view of Cullinan et al. (U.S. 5,457,113).

Barath, Thompson, Warri and Knabbe's teachings discussed as above.

The references do not teach the administration of the agent via stent.

Cullinan et al. teach that stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries and incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site (col. 5, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent as to inhibit smooth cell proliferation to treat atherosclerosis as taught by Barath et al. because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit smooth cell proliferation to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

Claim 164 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barath et al. (U.S. 5,242,397, filing date Jan 2 1992) and Thompson et al. (Br J Cancer, 1991, 63, 609-614 in view of Yang et al. (U.S. 5,219,548, filing date Oct 1 1990) as applied to claims 153, 154, 158-163, 174-176, 181-184 above and further in view of Cullinan et al. (U.S. 5,457,113).

Barath, Thompson, Yang et al. teachings discussed as above.

The references do not teach the administration of the agent via stent.

Cullinan et al. teach that stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries and incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site (col. 5, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer an agent as to inhibit smooth cell proliferation to treat atherosclerosis as taught by Barath et al. because of the teachings of Cullinan et al. One having ordinary skill in the art would have been motivated to administer an agent as to inhibit smooth cell proliferation to prevent the collapse and reocclusion of the coronary arteries and to deliver the drug directly to the proliferative site.

Response to Arguments

Applicant's arguments with respect to the rejections of the claims have been considered but are moot in view of the new grounds of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Shengjun Wang/
Primary Examiner, Art Unit 1627